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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/913,853	12/20/2001	Peter Andrews	033236-0116	5475

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	10

DATE MAILED: 09/12/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/913,853	ANDREWS ET AL.	
	Examiner	Art Unit	
	Thái-An N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 June 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *12,14,17,21,25,26,28 and 30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,15,16,18-20,22-24,27 and 29* is/are rejected.

7)☒ Claim(s) *2,9,12,14,17,25,26,30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-30 are pending. Claims 1-11, 13, 15, 16, 18-20, 22-24, 27 and 29 are under current examination. Claims 21 and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Election/Restrictions

Applicant's election with traverse of Group I [claims 1-20, 22, 24, 26 and 30] in Paper No. 9 is acknowledged. The traversal is on the ground(s) that Groups I, III and IV all share the same special technical feature, which is the defined content of the cell nucleus and cytoplasm. See pp. 1-2, bridging ¶ of Applicants' Response filed 6/27/03, Paper No. 9. Applicants' Arguments are found to be persuasive. As such, Groups I, III and IV will be examined together. Claims 1-20, 22-27, 29 and 30 are under current examination.

Claims 21 and 28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 9.

Claim Objections

Claims 2-10 are objected to because the claims all begin with "A cell according to claim ...". This is inappropriate because there is only one cell that the claim refer to. This objection can be overcome by using the language, "The cell according to claim ...".

Claim 9 is objected to because of the following informalities: the term *pluripotential* is misspelled in line 2 of the claim. Appropriate correction is required.

Claim 12 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from any other multiple dependent claim. See MPEP § 608.01(n). Accordingly, claim 12 and dependent claims 14, 17, 25, 26 and 30 have not been further treated on the merits.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, 13, 15, 16, 18-20, 22-24, 27 and 29 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such

a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to cells having a single nucleus, wherein the cell possesses at least one pluripotential characteristic, which characteristic includes the ability to differentiate into at least two selected tissue types, wherein the cell comprises either (i) at least part of the cytoplasm derived from an embryonal teratocarcinoma cell, or (ii) a cytoplast from a teratocarcinoma cell, wherein the cell has its nucleus obtained from a differentiated somatic cell and only contains the genome derived from the differentiated somatic cell. In further embodiments, the claims are directed to methods of producing a cytoplasmic part for use in the production of the claimed cell, by providing at least one embryonal teratocarcinoma cell, separating at least part of the cytoplasm from the nucleus of said cell, isolating said cytoplasmic part and optionally storing said isolated cytoplasmic part under suitable storage conditions.

The specification teaches the generation of pluripotent cells comprising at least part of the cytoplasm from a teratocarcinoma cell, and the nucleus of a somatic cell. The specification teaches that teratomas [tumors which contain a wide range or more or less organized tissues] typically occur as gonadal tumors [see p. 5, lines 16-24]. These embryonic carcinoma [EC] cells were found to resemble early embryonic cells and it was found that EC cells were able to generate a range of differentiated cells. See pp. 6-7. The specification teaches the generation of a

cybrid [a cell comprising at least a part of its cytoplasm from an EC cell] combined with the nucleus of a somatic cell, wherein the cybrid has pluripotent characteristics that allow it to differentiate into at least one selected tissue type. See p. 10.

The specification specifically teaches the preparation of mouse thymocytes, which were then fused using polyethylene glycol [PEG] to human EC cells. The fused cells were plated and after 2 days, the non-attached cells were aspirated. The remaining cells were harvested and RNA isolated and quantified. The cells were then analyzed for the expression of Oct-4 by PCR. See p. 18-20. The specification teaches the enucleation of EC cells by cytochalasin B to generate cytoplasts. The specification teaches that re-programmed embryonic stem [RPES] cells can be made by fusing two or more cells of different origins. Following the production of the RPES cells, additional methods are required to propagate the cells, characterize their properties, and induce them to differentiate into required somatic cell types. See p. 22-23, 25-31. The specification teaches that a large range of somatic cells may be used as nuclear donors, and that a large number of human EC cell lines have been isolated which can be used in the claimed methods. See pp. 24-25. The specification teaches that human Oct4 expression was detected in the thymocyte fused cells, as well as in the mock fusion experiment, which is consistent with the human Oct4 expression in the human EC cells. It was found that mouse Oct4 was detected in only the human-mouse fused cells. See pp. 33-34. The specification

further teaches that in a second experiment, where human 2102Ep and TERA1 EC cells were fused with mouse thymocytes, mouse Oct4 was detected in the fusion of the 2102Ep cells, suggesting that the TERA1 cytoplasm did not achieve reprogramming. See p. 34, lines 1-4.

The specification fails to provide teachings or guidance with regard to the claimed invention to show that the cells produced by the claimed method are pluripotent, as required by the claims. Note that the product claims (claims 1-11, 20, 22-25, 27 and 29) have been included in this rejection because they encompass pluripotent cells made by the claimed method. The specification clearly teaches that the claimed methods would be used to produce pluripotent cells. See p. 7, lines 17-18, for example. However, the only teachings provided by the specification show that the expression of mouse Oct4 in the experiments involving the fusion of the human EC cell line, 2102Ep and mouse thymocytes which the specification concludes indicates that the mouse thymocytes were reprogrammed. However, the specification teaches another human EC cell line, TERA1, was unable to reprogram the mouse thymocytes, as shown by the lack of expression of mouse Oct4. As such, the specification teaches only one example to show reprogramming in mouse thymocytes, as evidenced by the expression of Oct4. However, it is known in the art that the expression of Oct4 is not necessarily an indicator of pluripotency. For example, Monk and Holding [**Oncogene**, 20:8085-8091 (2001)] found that Oct4 is expressed in human tumors. See *Abstract.* Monk & Holding compare the

expression of embryo-specific genes in tumor and normal tissues [see Figure 3] and found that the known embryonic gene, Oct4, was expressed in the panel of tumors, and at high levels in blastocyst and cancer cells, but at much lower levels in normal tissue. See Figure 5. As such, the art supports that although Oct4 is recognized as an embryonic gene, the mere detection of expression of Oct4 is not an indicator of pluripotency, because tumor tissues, as well as normal tissues, express Oct4.

The specification further teaches that primate ES cells exhibit a range of characteristics or markers that are associated with pluripotency. For example, specific cell surface markers [SSEA-3 (+), SSEA-4 (+), TRA-1-60 (+), TRA-1-81 (+)], have stable karyotypes, continue to proliferate in culture in an undifferentiated state, and have the ability to differentiate into all three embryonic germ layers [see p. 3, lines 16-23]. Furthermore, the specification teaches that primate ES cell lines show high levels of telomerase activity [see p. 3, lines 25-29], and that a pluripotential characteristic is a chromosomal methylation pattern characteristic of pluripotential cells [pp. 9-10, bridging ¶], and that the cells when introduced into an animal, have the ability to induce tumors into the animal [p. 10, lines 11-13].

However, the specification fails to provide specific teachings or guidance to show that the methods of the claimed invention would, indeed, produce cells that are pluripotent. The specification's showing of Oct4 expression in the fused heterokaryons is not enabling, as shown *supra*, that the mere expression of Oct4 is not necessarily indicative of pluripotency. The specification fails to teach that the

cells of the claimed invention express specific cell surface markers that are indicative of pluripotent cells, that the cells of the invention show high levels of telomerase activity, are methylated in a pattern characteristic of pluripotent cells, or are able to induce tumors when introduced in an animal, as required by the claims. As such, the specification fails to provide an enabling disclosure for the generation and use of the claimed cells.

It is noted that certain of the claims are directed to methods which generate a nuclear transfer unit, wherein the NT unit is further cultured under conditions to proliferate and expand the NT unit. See part (iii) of claim 13, for example. However, it is well known in the nuclear transfer art that activation of the resulting nuclear transfer unit must take place in order to effect further development; however, the claims do not provide such steps. Dinnyés *et al.* [**Cloning & Stem Cells**, 4:81-90, 2002] report on the state of the art of somatic cell nuclear transfer state that, "NT is a complex procedure and each step effects the overall efficiency. The unpredictability of the technology due to biological variation of the recipient oocytes and the donor cells is difficult to control. Therefore, standardization of the steps is important in order to obtain consistent results." [See p. 83, 1st column, 2nd full paragraph]. With particular regard to the importance of the activation of oocytes, Dinnyés *et al.* state that, "In NT, the lack of sperm-induced fertilization steps necessitate the application of an artificial activation in order to trigger further development." [See p. 83, 2nd column, last paragraph].

The specification fails to provide teachings to show the exemplified methods would produce a cell with a pluripotential characteristic, which includes the ability to differentiate into at least two selected tissue types, as required by the claims. The specification further fails to show that using an EC cell as a cytoplast recipient in a nuclear transfer method would result in the generation of cells which would be considered pluripotent. For example, the specification fails to teach or provide guidance to show that the RPES cells of the instant invention would further develop such that they could differentiate. The state of the art of nuclear transfer teaches that in successful NT methods, the recipient cell [cytoplast] can be an oocyte, fertilized zygote or two-cell embryo, cells which are able to support further development of the NT unit. For example, Campbell *et al.* [**Cloning & Stem Cells**, 3(4):201-208, 2001] teach that:

> *Oocytes, fertilized zygotes, and two-cell embryos have been used as cytoplast recipients for NT. In general, oocytes arrested at metaphase of the second meiotic division have become the cytoplast of choice. At this point in oocyte development, the genetic material is arranged upon the meiotic spindle and is easily removed using mechanical means ... The use of fertilized zygotes as cytoplast recipients has been reported in mouse, cattle and pigs. In all three species, development of embryos constructed using zygotes as cytoplast recipients was low, and on the whole, restricted to the exchange of pronuclei, suggesting that factors essential for successful development are removed with the pronuclei.* See p. 202, 2nd column, ***The Recipient Cell or Cytoplast.***

The instant invention requires that the cells produced by the claimed method be able to differentiate into at least two tissue types, thus, the cell requires further

development, which, as supported by the art, would be possible utilizing, for example, an oocyte. Although the specification provides general teachings with regard to how the fused EC/differentiated cell would be grown and selected, see pp. 28-29, the specification fails to show that an EC would support further development, such that the cells would pluripotent and be able to differentiate into at least two selected tissue types.

Furthermore, with regard to claim 7, the claim is directed to a cell comprising at least part of the cytoplasm derived from an EC combined with a nucleus of a differentiated cell, wherein the cell express Oct 4. The claim, as written, describes a nuclear transfer unit wherein the NT unit expresses Oct4. The specification fails to provide teachings or guidance to show that the nuclear transfer unit, as claimed, would indeed express Oct-4. For example, the specification teaches the heterokayon fusion of human EC cells and mouse thymocytes, the cells were first fused and then plated and incubated for 2 days. After 2 days, the non-attached cells were aspirated and the remaining cells were analyzed by PCR for the expression of Oct-4. See pp. 15-16. The specification teaches that the expression of Oct-4 indicates the reprogramming of a somatic cell nucleus to an ES/EC cell like state [see p. 28, lines 16-19]. The specification teaches that, "Following fusion to combine a differentiated cell and an ES/EG cell, with prior or subsequent removal of the ES/EG cell nucleus, it is necessary to provide appropriate conditions for the re-programming of the differentiated cell nucleus and the subsequent proliferation of the resulting RPES

[Reprogrammed Embryonic Stem] cells." See p. 24, lines 15-18. As such, the specification provides support for cells cultured from the NT unit that express Oct-4, however, the specification fails to provide sufficient teachings or guidance to show that the nuclear transfer unit itself would express Oct-4, as the specification clearly teaches the growth and proliferation of the original nuclear transfer units for 2 days before analysis for Oct-4 expression.

Accordingly, in view of the lack of specific teaching or guidance provided by the specification with regard to the pluripotency of the cells produced by the nuclear transfer methods, other than the mere expression of Oct4, the state of the art, which teaches that Oct4 is expressed in normal, cancerous and embryonic tissues, the requirement for activation of the nuclear transfer unit to produce a successful nuclear transfer, it would have required undue experimentation for one skilled in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1, as written, is indefinite. The claim recites that the cell has, "the ability" to differentiate into at least two selected tissue types. See lines 2-3 of the claim. This describes a latent property, and it is unclear whether this actually

occurs or not. "The ability" implies a latent property and the conditions for the latent property must be clearly defined. Therefore, it is unclear if the latent property is ever obtained. Claims 2-11, 13, 15, 16, 20, 23 and 29 depend from claim 1.

Claim 5, as written, is indefinite. The claim recites that the cell has "the capacity" to proliferate [see lines 1-2 of the claim]. "Capable of" describes a latent property, and it is unclear whether this property occurs or not.

Claim 9, as written, is vague. The claim recites that the cell, "includes the presence of a chromosomal methylation pattern characteristic of pluripotential cells". This is unclear because it would not be expected that all types of pluripotent cells would express the same methylation pattern. For example, would adult pluripotent stem cells have the same methylation pattern as other pluripotent stem cells? Clarification and/or amendment to the claim is requested.

Claim 20 is unclear. The claim recites, "at least one cell according to any of claims 1." It is unclear if the claim refers to more than one claim, or just claim 1. Clarification and/or amendment is required.

Claims 22 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite in that it fails to point out what is included or excluded by the claim language. The claims recite the cell "according to the invention." This claim is an omnibus type claim.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thái-An N. Ton whose telephone number is (703) 305-1019. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to William Phillips, Patent Analyst, at (703) 305-3482. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703)-872-9306.

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